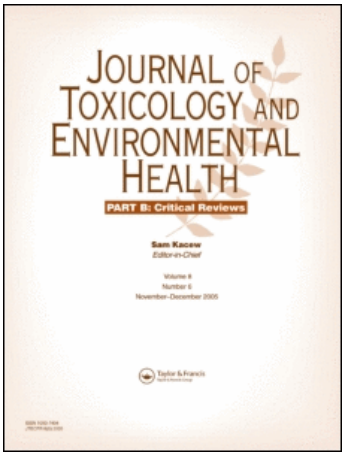

Journal of Toxicology and Environmental Health, Part B
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713667286

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To cite this Article Bondy, Genevieve S. and Pestka, James J.(2000) 'IMMUNOMODULATION BY FUNGAL TOXINS', Journal of Toxicology and Environmental Health, Part B, 3: 2, 109 — 143
To link to this Article: DOI: 10.1080/109374000281113
URL: http://dx.doi.org/10.1080/109374000281113

Journal of Toxicology and Environmental Health, Part B, 3:109–143, 2000

1093-7404/00 $12.00 + .00

IMMUNOMODULATION BY FUNGAL TOXINS

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The availability of immunotoxicity data for fungal toxins varies considerably for different toxins. The following is a comprehensive review of the most recent literature on the immunotoxicity of aflatoxins, fumonisins, gliotoxin, ochratoxins, patulin, and trichothecenes. Aflatoxin is an immunomodulating agent that acts primarily on cell-mediated immunity and phagocytic cell function. In addition to further characterization of aflatoxin-induced immunotoxicity in various species, some recent studies have focused on ameliorating the effects of aflatoxin by supplementing or amending the diet. The immunomodulatory effects of ochratoxins have also been considered for many years. Notably, recent studies have examined immune function in the offspring of rats and mice exposed to ochratoxin pre- and perinatally. Fumonisin toxicity has been characterized relatively recently in comparison to aflatoxin and ochratoxin, and fumonisin-induced immunotoxicity is an area of active research. As these studies progress, they may also clarify the role of sphingolipid metabolism in immune function. The most recent study of patulin immunotoxicity in mice indicates that exposure to levels found in foods and feeds would not likely result in immunotoxicity. Exposure to gliotoxin would most likely be by infection with gliotoxin-producing fungi. Although the toxin is immunosuppressive in vitro, the link between immunosuppression and the presence of gliotoxin in infected tissues in vivo has yet to be made. The trichothecenes can both suppress and stimulate immune function. By comparison, more information is available on the molecular events associated with trichothecene-induced immunomodulation than for any other fungal toxins. The molecular basis of immune function modulation by fungal toxins remains a frontier for future research.

The ability of naturally occurring or anthropogenic food and environmental contaminants to alter immune function in animals and humans has been the subject of increasing interest in recent years. The recognition that immunotoxicology is an important element when considering potential adverse effects of chemical exposure has resulted in the compilation of pro-

This work was supported by Health Canada (GSB) and by Public Health Service Grants ES-03358 (JJP) and ES-09521 (JJP) from the National Institute for Environmental Health Sciences. Special thanks to Dr. Doug Arnold and Paul Rowsell for their suggestions and comments.

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posed guidelines for immunotoxicity testing by various organizations. These guidelines are generally meant to be followed in conjunction with strategies for short and long term toxicity testing. The Organization for Economic Cooperation and Development (OECD) has incorporated basic immunotoxicological endpoints into its Guideline 407, "Repeated dose 28-day oral toxicity study in rodents", including weights of immune organs, blood cell counts, and histopathology of immune organs such as spleen and thymus. Expanded immunotoxicity testing guidelines have been put forth by other organizations, including the U.S. National Toxicology Program, the Dutch National Institute of Public Health and Environmental Protection, the U.S. Food and Drug Administration, and the U.S. Environmental Protection Agency. These proposed guidelines have been reviewed by the International Programme on Chemical Safety (1996). Most guidelines are designed for a rodent model, either the rat or the mouse, and are intended to provide data that can be extrapolated for assessing the risk of immunotoxicity posed by human exposure to chemicals. Additionally, at least one testing strategy has been proposed for poultry immune assessment (Dietert et al., 1994). In addition to the basic endpoints mentioned already, most proposed guidelines include measures of specific aspects of the immune system. These include antibody responses to sheep red blood cells (SRBC) (humoral immunity); natural killer cell activity and macrophage function (innate or nonspecific immunity); lymphoproliferative responses to T-cell antigens and delayed-type hypersensitivity responses (cellular immunity); and infectivity or host-resistance challenges.

A comprehensive approach to immunotoxicity testing is not standard for fungal toxins. For some toxins, for example, ochratoxin and aflatoxin, the available literature provides a considerable volume of information on immunotoxicity. In many cases immunotoxicity endpoints have been explored to different degrees in multiple species, including rodents, poultry, pigs, and occasionally larger livestock, and a complete view of the immunotoxicity of these contaminants can only be gained from compiling the data from many sources. The lack of concerted effort to establish fungal toxin immunotoxicity according to proposed guidelines is likely related to the degree of variation between countries in (1) the regulations for mycotoxins in foods and feeds (Van Egmond, 1989) and (2) the scientific basis for mycotoxin regulations (Stoloff et al., 1991). A comprehensive database on the hazards associated with each mycotoxin would be a valuable asset in coming to an international consensus on mycotoxin regulations (Stoloff et al., 1991). With this in mind, the following is a compilation and review of the most recent literature on fungal toxin immunotoxicity. Previous reviews have covered this subject for earlier time periods (Pestka & Bondy, 1994; Pier, 1986; Richard, 1991; Thurston et al., 1986). Until there is agreement on an immunotoxicity testing strategy for mycotoxins, it is critical that the wide variety of available information be periodically compiled and reviewed.

Aflatoxins

Aflatoxins, which are secondary metabolites of molds including *Aspergillus flavus* and *A. parasiticus,* have a long history of association with illness and disease in poultry and domestic animals. Although hepatic lesions are the endpoint most associated with aflatoxicosis, many studies have shown that these toxins are also immunomodulatory. Past studies have clearly shown that cell-mediated immunity and phagocytic cell functions (innate immunity) are affected by aflatoxins to a greater extent than humoral immunity in most test species, and this has not been contradicted by recent studies. Recent advances in the area of aflatoxin-induced immunotoxicity include studies of the effects of maternal aflatoxin exposure on offspring, as well as further work on the potential for amelioration of aflatoxin-induced toxicity using dietary manipulation or supplementation.

In poultry exposed to aflatoxin-contaminated feed, many studies have verified that cell-mediated immune responses are a target (Ali et al., 1994; Neiger et al., 1994; reviewed by Pestka & Bondy, 1994). The question of whether or not the progeny of poultry exposed to aflatoxin in the diet could also suffer compromised immune function was addressed by Qureshi et al. (1998). Broiler hens received aflatoxin-contaminated diet (0.2 to 5 mg/kg AFB_1) for 14 d and eggs were collected up to 3 wk after feeding. Cell-mediated, humoral and phagocytic functions were compromised in the offspring. Progeny chicks had decreased titers 7 d after injections of the T-dependent antigen sheep red blood cells (SRBC) (0.2 to 5 mg/kg AFB_1). Titers to the T-independent antigen *Brucella abortus* were also significantly decreased (5 mg/kg AFB_1), as were numbers and phagocytic abilities of peritoneal macrophages (Qureshi et al., 1998). Embryonic exposure was confirmed by the detection of aflatoxin and aflatoxicol in eggs from hens given 10 mg aflatoxin/kg feed (Qureshi et al., 1998). This confirms the results of studies in which direct administration of AFB_1 to chick embryos in ovo caused dose-related decreases in phagocytic abilities in peritoneal macrophages (Neldon-Ortiz & Qureshi, 1992).

Similarly, the immune system of developing pigs has been shown to be affected by exposure of sows to AFB_1 (800 ppb), AFG_1 (800 ppb), or both (400 ppb each) during gestation and lactation (Silvotti et al., 1997). Aflatoxins were detected in milk from treated sows at levels up to 532 ppt on d 25 after birth, when the piglets were sacrificed. Blood lymphocyte proliferation due to phytohemagglutinin (PHA), a T-cell mitogen, was depressed in aflatoxin-exposed piglets. Phagocytic functions were unaffected in monocyte-derived macrophages, but the oxidative burst was inhibited. Neutrophil function, including motility and chemotaxis, was inhibited in piglets from aflatoxin-treated sows. In a similar study, thymus weight was decreased and thymic cortical lymphocytes were depleted in piglets from exposed sows (Mocchegiani et al., 1998). The bioavailability of zinc may play a role in altered cell-mediated immunity, since changes to the piglet thymus were associated with depressed plasma Zn levels and decreased plasma levels of

biologically active Zn-dependent thymic hormone (Mocchegiani et al., 1998).

The effects of aflatoxin on weanling rats have been shown to be similar to those observed in adult rats (Raisuddin et al., 1993). Five- to 6-wk-old rats received AFB_1 (60 to 600 μg/kg body weight) orally every other day for 4 wk. The cellular immune system was most affected. The delayed-type hypersensitivity response to SRBC, measured by foot-pad thickness, was significantly inhibited in AFB_1-treated rats, as were lymphoproliferative responses to PHA. Humoral responses were either unaffected (antibody responses to SRBC), or affected to a lesser extent than cellular responses [lipopolysaccharide (LPS)-induced lymphocyte proliferation].

Economic losses due to aflatoxin-induced decreases in performance and health are a powerful incentive to reduce or prevent the effects of contaminated feed on domestic animals. Nutritional factors can influence the effects of mycotoxins, including aflatoxins (Newberne, 1987). In a 28-d feeding study, dietary supplementation with 0.15% DL-methionine ameliorated weight-gain depression in pigs given 182 ppb AFB_1 in the diet (Coffey et al., 1989). In a 21-d feeding study, dietary supplementation with 0.15% to 0.45% DL-methionine did not improve the immune responses in aflatoxin-treated pigs (van Heugten et al., 1994). As in other species, dietary aflatoxin (280 ppb) inhibited cellular immune responses in pigs, measured as reduced skin thickness in response to injected PHA. Humoral effects were inconsistent, as dietary aflatoxin stimulated LPS-induced lymphocyte proliferation but antibody responses to SRBC were unaffected (van Heugten et al., 1994). In addition to dietary manipulation, other approaches have been examined for ameliorating the toxic effects of AFB_1. *Staphylococcus aureus* protein A, which protects against carbon tetrachloride and cyclophosphamide toxicity, was investigated for its potential to prevent aflatoxin-induced immunotoxicity in rats (Raisuddin et al., 1994). Rats were given 7 oral doses of AFB_1 (300 μg/kg body weight) over a 2-wk period. Protein A was injected intravenously (iv) twice a week for 2 wk and was administered either before, after, or both before and after AFB_1 treatments. Protein A either partially or completely negated changes in the following immunotoxicity endpoints: (1) thymus and bone marrow cellularity; (2) PHA- and LPS-induced lymphocyte proliferation; (3) numbers and phagocytic ability of peritoneal macrophages; and (4) delayed-type hypersensitivity responses measured by foot-pad thickness. Raisuddin et al. (1994) suggested that the protective effects of protein A may be related to its immunostimulatory properties, its antioxidant properties, its ability to regenerate depleted metabolic enzymes, or some combination of all of these qualities. In support of these findings, Zaky et al. (1998) found that a combination of Freund's complete adjuvant (FCA), which activates the reticuloendothelial system, and protein A protected chickens from the hepatotoxic effects of AFB_1. This points to a connection between hepatotoxicity and immunosuppression, which can be overcome by stimulating the immune

system. Such studies are useful as indicators of possible strategies for reducing economic losses when livestock and poultry are exposed to immunosuppressive fungal toxins, and as a means of investigating the mechanism of action of fungal toxins.

Studies in laboratory animals have shown that aflatoxin-induced immunosuppression increases the risk of secondary infection (Pier, 1986). In a recent study, aflatoxin ingestion was shown to activate infection in mice preinfected with the cyst-forming parasite *Toxoplasma gondii* (Venturini et al., 1996). Mice were injected with the parasite 1 mo before feeding studies commenced. Aflatoxin (0.1 mg/kg body weight) was administered by gavage daily for 50 d. The parasite formed cysts in the brain of immunocompetent control animals, but the infection was latent. In contrast, aflatoxin-treated mice had ruptured cysts and brain lesions indicative of compromised immune function. In addition to increased infectivity, studies in poultry have shown that exposure to aflatoxin in the diet at levels of 200 ppb AFB_1/d for up to 40 wk reduces antibody titers to vaccines (Azzam & Gabal, 1998; Gabal & Azzam, 1998). In rabbits, aflatoxin reduces antibody titers to *Mycobacterium bovis* (Gabal & Dimitri, 1998) and can cause false negative responses to the tuberculin test. Skin reactions both to *Bacillus* Calmette and Guerin (BCG) and to killed *M. bovis* were significantly decreased in rabbits given 2 ppm AFB_1 in feed for 5 wk (Dimitri & Gabal, 1996).

In vitro assays offer a convenient means of studying the effects of fungal toxins on human cells. Inhibition of phagocytic cell function has been observed in many species exposed to aflatoxin. Cusumano et al. (1996) confirmed that human phagocytic cell functions were also vulnerable to aflatoxin-induced toxicity. Aflatoxin B_1 was cytotoxic to human peripheral monocytes in the 0.1 to 1 ng/ml range. At concentrations of 0.5 and 1 pg AFB_1/ml, phagocytic activity was inhibited, as was intracellular killing of *Candida albicans;* however, superoxide production and the ability to destroy intracellular herpes simplex virus were unaffected.

Recent studies indicate that effects on hematopoietic cells may contribute to AFB_1-induced immunomodulation in vivo. Interleukin-1 (IL-1) production by peritoneal macrophages from rats given a single intraperitoneal (ip) injection of 1 mg/kg AFB_1 increased 1 d after dosing (Cukrová et al., 1992). Bone marrow cell colony-stimulating activity (CSA) was also increased along the same time course as IL-1. In conjunction with these changes, numbers of bone marrow colonies were transiently decreased at 1 and 2 d postdosing, and then increased along with IL-2 production at 3 and 4 d post-AFB_1. This would appear to contradict the inhibition of bone marrow granulocyte–macrophage progenitor cell colonies observed in mice exposed to AFB_1 by gavage at doses of 0.03 to 0.7 mg/kg body weight every other day for 2 wk (Dugyala et al., 1994). Additionally, Walsh et al. (1991) found that AFB_1 did not affect the ability of bovine macrophages to produce IL-1 in vitro and ruled out IL-1 involvement in AFB_1-induced inhibition of bovine macrophage proliferation. Given the

complexity of the processes being measured, apparent differences in aflatoxin-induced modulation of the complex interplay between cytokine production and immune cell activation and suppression will be difficult to reconcile in studies with widely varying routes, doses, and dosing regimens. However, in general these data indicate that modulation of cytokine production and timing may play an important role in the immunomodulatory effects of aflatoxin. The observation of a mitogenic effect in human peripheral T_4 lymphocytes exposed in vitro to aflatoxin concentrations ranging from 10 to 100 μg/ml (Griffiths et al., 1996) is further indication that the effects of aflatoxins on the immune system may be immunomodulatory rather than simply immunosuppressive.

Fumonisins

The fumonisin toxins are produced primarily by *Fusarium verticilliodes* and *F. proliferatum* (Bacon & Nelson, 1994). Of particular note is the apparent species specificity of fumonisin toxicity. Purified fumonisin B_1 (FB_1) causes leukoencephalomalacia in horses (Marasas et al., 1988) and pulmonary edema in pigs (Harrison et al., 1990). In mice the primary target is the liver, whereas in rats the kidneys are more sensitive (Gelderblom et al., 1991; Voss et al., 1993, 1995). In spite of these species differences, the available data on immunotoxicity indicate that fumonisin-induced changes in immune function are not species specific, and appear to involve aspects of humoral, cellular, and innate immunity.

Poultry are relatively resistant to the effects of fumonisins and show few signs of toxicity after ingestion of feed contaminated with less than 75 mg FB_1/kg feed. Hepatic changes, including hepatocellular hyperplasia, were the most notable changes in ducklings or turkey poults ingesting feed contaminated with greater than 75 mg FB_1/kg (Bermudez et al., 1995; Ledoux et al., 1996). Fumonisin-associated immunotoxicity has been seen in birds ingesting feed contaminated with mycotoxins including fumonisins. Ingestion of diets amended with up to 25% corn cultures contaminated with an isolate of *F. moniliforme* associated with equine leukoencephalomalacia manifested as depressed thymus weights and depressed antibody responses to SRBC and *Brucella abortus* in chickens (Marijanovic et al., 1991). Fumonisin levels were not determined, although the presence of fusarin C in culture materials indicated that immunotoxic effects could not be attributed to fumonisins alone. Chicks ingesting feed contaminated with a mixture of FB_1 (61–546 ppm), FB_2 (14–98 ppm), and moniliformin (66–367 ppm) had dose-related reductions in titers to Newcastle disease vaccine in conjunction with decreased serum globulins (Javed et al., 1995). Turkey poults ingesting feed contaminated with *F. moniliforme* culture material containing fumonisins at levels of 100 or 200 mg/kg feed displayed lesions indicative of immunotoxicity, including diffuse thymic cortical thinning, mild bursal follicular atrophy, and mild splenic lymphocyte depletion (Weibking et al., 1993). There is limited evidence that ingestion of culture

material contaminated with lower fumonisin levels is immunotoxic to poultry. In chickens ingesting feed contaminated with FB_1 (61 ppm), as well as FB_2 (14 ppm) and moniliformin (11 ppm), antibody responses to SRBC were depressed 14 d after the first injection and 7 d after the second injection, but were increased 14 d after the second injection. Peritoneal macrophage numbers and phagocytic ability were also compromised (Qureshi et al., 1995). Data on the immunotoxicity of purified FB_1 in poultry are limited. Reduced white blood cell (WBC) counts in chicks given 125 or 274 ppm FB_1 in feed (Javed et al., 1995) indicate that some immunotoxic effects associated with fungal toxin-contaminated feeds are attributable to fumonisins, albeit at relatively high concentrations.

In pigs, ingestion of fumonisin-contaminated corn at levels of 33 mg/kg for 21 d resulted in suppressed lymphocyte blastogenesis and titers to pseudorabies virus at d 14 but not at d 21 (Osweiler et al., 1993b). Lymphocyte blastogenesis was also suppressed in pigs given fumonisin-contaminated culture material at levels resulting in 100 mg FB_1/kg feed (Harvey et al., 1996), and after 28 d PHA-induced lymphocyte blastogenesis was suppressed.

In calves, ingestion of feed experimentally adulterated with fumonisin-contaminated corn screenings containing up to 148 μg/g total fumonisins inhibited neutrophil migration but not phagocytosis or antibody-dependent cytotoxicity. Mitogen-stimulated [concanavalin A (ConA), PHA, and pokeweed mitogen (PWM)] lymphocyte blastogenesis was inhibited, while in vitro antibody production by lymphocytes and serum complement and conglutinin activity were unaffected (Osweiler et al., 1993a).

Recently rodent models have been used to address fumonisin immunotoxicity. Only one study to date addresses the potential immunotoxicity of purified FB_1 using oral exposure. Tryphonas et al. (1997) administered FB_1 by gavage at doses from 1 to 25 mg/kg body weight/d for 14 d to Sprague-Dawley rats. This treatment caused depressed responses to SRBC at the 25-mg/kg dose level, and a significant trend toward increased numbers of colony-forming bacteria in the spleens of rats experimentally infected with *Listeria monocytogenes*. There were no marked effects on spleen lymphocyte blastogenesis, calcium mobilization in ConA-stimulated lymphocytes, natural killer (NK) cell activity, or peripheral blood monocyte phagocytic activity.

In general, mice were not as sensitive to FB_1 as rats (Bondy et al., 1996, 1997, 1998). In gavage studies, mice given 1 to 75 ppm purified FB_1 for 14 d showed minimal signs of immunotoxicity. A few females had mild thymic cortical lymphocytolysis in the 35- and 75-mg/kg dose groups, and there were significant numbers of vacuolated bone-marrow cells including lymphocytes, but there were no marked changes in the spleen or lymph nodes and no changes in numbers of circulating blood cells or serum total immunoglobulins (Bondy et al., 1997). A single study of responses to SRBC in mice injected ip with purified FB_1 was inconclusive.

Changes were dependent on the sequence of exposure to the toxin and SRBC (Martinova & Merrill, 1995). When FB_1 (1 to 50 μg per dose) was injected daily for 5 consecutive days starting on d 0 and SRBC were injected once on d 0, responses to SRBC increased significantly at d 3 and peaked at d 4. With the exception of the 50-μg FB_1 dose group, responses to SRBC dropped to control levels at d 5. A single dose of 5, 20, or 50 μg FB_1 injected once before or at the same time as the SRBC caused significant inhibition of antibody responses to SRBC when measured 4 and 5 d after toxin injection.

In vitro studies have focused on the effects of FB_1 on macrophage function or on lymphocyte proliferation. Fumonisin B_1 extracted from *F. moniliforme*-infected corn kernels reduced the viability and phagocytic activity of chicken peritoneal macrophages at levels of 6 to 18 μg/ml in macrophage cultures (Chatterjee & Mukherjee, 1994). Microscopic examination revealed increased nuclear disintegration in treated macrophages (Chatterjee et al., 1995). This confirms earlier studies in which cytotoxicity, nuclear disintegration and cytoplasmic blebbing, and reduced phagocytosis were observed in chicken peritoneal macrophages exposed to FB_1 at concentrations of 0.5 to 10 μg in culture (Qureshi & Hagler, 1992). Fumonisin B_1 inhibits murine spleen lymphocyte and turkey peripheral lymphocyte proliferation at levels as low as 0.1 μg/ml (Dombrink-Kurtzman et al., 1994; Martinova & Merrill, 1995). In turkey lymphocytes, FB_2 was a more potent inhibitor of proliferation than FB_1 in vitro (Dombrink-Kurtzman et al., 1994); however, in vivo data from rats injected ip with either FB_1 or FB_2 indicate that FB_2 is, in general, slightly less toxic than FB_1 (G. Bondy, unpublished observations). The most striking morphologic change in turkey lymphocytes was cytoplasmic vacuolization in treated cells (Dombrink-Kurtzman et al., 1994). Similarly, bone-marrow lymphocyte cytoplasmic vacuolization has been observed consistently in rats and mice treated with FB_1 in vivo (Bondy et al., 1996, 1997, 1998).

Some of the immunomodulatory effects of fumonisins may be the result of changes in the expression of cell surface markers important in immune cell communication. In mice given a single ip injection of 5 or 20 μg FB_1, CD3 receptor expression and sphingomyelin levels were decreased in thymocytes but not in splenocytes (Martynova et al., 1995). Fumonisin-induced immunomodulation may also be due to changes in cytokine secretion. Selective induction of tumor necrosis factor (TNF)-α mRNA and secretion of TNF-α protein were observed in peritoneal macrophages from mice injected subcutaneously with FB_1 (0.25 to 6.75 mg/kg/d for 5 d). Interleukin-1α and interferon (INF) γ expression and secretion were unaffected (Dugyala et al., 1998).

In mammalian cells, FB_1 inhibits *N*-acyltransferase (ceramide synthase), which is the enzyme catalyzing the amide linkage of a fatty acid to sphinganine to form the complex sphingolipid dihydroceramide. This results in accumulation of substrate (free sphinganine) and depletion of prod-

uct (dihydroceramide), as well as increased products associated with free sphingamine metabolism (Wang et al., 1991; Riley et al., 1994). Sphingolipid metabolites are involved in multiple signal transduction pathways and in the generation of intracellular second messengers (Spiegel & Merrill, 1996). Fumonisin is structurally similar to the protein kinase C (PKC) inhibitor sphingosine, and has been shown to inhibit PKC activity in CV-1 (African green monkey kidney) cells (Huang et al., 1995) and to cause redistribution of PKC from cytosol to membrane in rat cerebral cortex slices (Yeung et al., 1996). In CV-1 cells fumonisin also inhibits the transcription of cyclin dependent kinase inhibitors and induces cell-cycle arrest (Ciacci-Zanella et al., 1998). In vivo, FB_1 has been shown to inhibit transcription of cyclin D1 and to increase transcription of the cyclin kinase inhibitor p27 in the livers of treated rats (I. Curran, unpublished observations). Since immune responses are critically dependent on intracellular signaling, the relationship between fumonisin-induced disruption of sphingolipid metabolism and immunomodulation requires further exploration. Fumonisin B_1 has been used as a tool to show that ceramide production is a part of the signal pathway involved in T-cell-receptor-induced IL-2 production and apoptosis (Tonnetti et al., 1999). The further use of FB_1 to study the role of sphingolipids in immune cell signaling will undoubtedly provide valuable data on the immunomodulatory effects of this toxin.

Gliotoxin

An antifungal agent, later designated gliotoxin, was first isolated from cultures of the fungus *Gliocladium* (Weindling & Emerson, 1936). Further studies revealed antibacterial and antiviral properties, although its toxicity ruled out clinical applications (Johnson et al., 1943; Rightsel et al., 1964; Taylor, 1971; Waksman & Woodruff, 1942). Although aflatoxin, vomitoxin, and fumonisin B_1 are ingested as food contaminants, only a single study to date has implicated gliotoxin as a food-borne toxin. Camels ingesting hay found to be contaminated with up to 495 µg/kg gliotoxin and 25 µg/kg ochratoxin A died with severe diarrhea accompanied by edema and hemorrhage in multiple organs (Gareis & Wernery, 1994). Exposure of animals and humans to gliotoxin appears more likely to occur as a result of toxin production during infection by several fungi that have been associated with disease states, particularly *Aspergillus fumigatus* and *Candida albicans*.

Mounting proof of the potential involvement of gliotoxin in the pathogenesis of fungal infections rests on evidence of gliotoxin production by organisms associated with cases of fungal infection in animals and humans. Gliotoxin was isolated from the udder of a cow naturally infected with *A. fumigatus* (Bauer et al., 1989). Lung tissues from turkey poults experimentally infected with an isolate of *A. fumigatus* originally isolated from an outbreak of avian aspergillosis were found to contain gliotoxin at levels ranging from 428 to 6024 ng gliotoxin/g tissue (Richard & DeBey, 1995). Gliotoxin was also isolated from lung tissues obtained from turkeys with "airsaccu-

litis," which were found to be infected with gliotoxin-producing strains of *A. fumigatus*. Although only three out of six tissue samples contained both *A. fumigatus* and gliotoxin, and gliotoxin was also found in two tissue samples from which *A. fumigatus* was not isolated, the data still suggest a correlation between gliotoxin and aspergillosis pathogenesis in turkeys (Richard et al., 1996). In a mouse model of aspergillosis, gliotoxin has been identified in peritoneal lavage samples from animals infected with *A. fumigatus* (Eichner et al., 1988).

Evidence of gliotoxin involvement in human disease is not yet as strong. Cultures of the fungus *Thermoascus crustaceous* isolated from monocyte cultures from the blood of AIDS patients were found to produce gliotoxin (Sell et al., 1983; Waring et al., 1988). Gliotoxin was identified in cultures of *Candida albicans* isolated from the vaginal fluid of women receiving gynecological care; however, none of the subjects had symptoms of yeast infection at the time the samples were collected (Shah & Larsen, 1992). Stronger evidence of a connection between gliotoxin and yeast infection pathogenesis comes from the detection of gliotoxin in vaginal swabs of patients with vaginal *Candida* infection (Shah et al., 1995).

The immunosuppressive properties of gliotoxin were first identified in vitro. Macrophage adherence to plastic and phagocytosis were inhibited at 20–50 ng gliotoxin/ml (Müllbacher & Eichner, 1984). Incubation of stimulator cells in mixed lymphocyte cultures with gliotoxin (100 and 1000 ng/ml) inhibited their ability to induce alloreactive cytotoxic T cells. At the lower toxin concentration, gliotoxin interfered with interleukin-related events, since addition of supernatant from ConA-stimulated lymphocytes restored the ability of stimulator cells to induce cytotoxic T cells. Gliotoxin did not inhibit antibody and complement-mediated cell lysis of treated target cells and thus does not appear to affect surface antigenic structures (Müllbacher & Eichner, 1984). Further in vitro effects include inhibition of mitogen-stimulated mouse spleen and bone marrow cell proliferation (Müllbacher et al., 1986, 1987; Seigle-Murandi et al., 1990) and inhibition of mitogen-stimulated turkey peripheral blood lymphocyte proliferation (Richard et al., 1994). Structurally, absence of the disulfide bridge in toxins related to gliotoxin renders the compound inactive (Müllbacher et al., 1986). Lipophilicity is also an important quality. The structurally related but more lipophilic fungal toxin sporidesmin is more toxic in vitro than gliotoxin (Middleton, 1974).

Experimental evidence of in vivo immunosuppression by gliotoxin is limited. In acute toxicity studies with hamsters the primary target was the liver and not the immune system. A single ip dose of 15 to 35 mg/kg gliotoxin caused necrotizing and proliferative cholangitis. Mild to moderate splenic lymphocyte necrosis was present in some animals but was not dose related (Frame & Carlton, 1988). In mice immunosuppressed by sublethal irradiation, ip injection of gliotoxin (100 μg) delayed the reappearance of splenic B lymphocytes. Apoptotic cells were observed in the spleen, thy-

mus, and lymph nodes of immunosuppressed mice receiving 100 or 200 μg gliotoxin. None of these effects were seen in control, nonirradiated mice (Sutton et al., 1994). Gliotoxin treatment of donor bone marrow and lymph node cells suppressed graft-versus-host responses in irradiated mice transplanted with these cells (Müllbacher et al., 1987).

Experimental evidence strongly supports a role for gliotoxin as an immunotoxic agent; however, proof of in vivo immunosuppressive activity as a result of intoxication associated with fungal infection is not yet conclusive. Until in vivo endpoints indicative of immunosuppression are clearly linked both to infection with gliotoxin-producing fungi and to the presence of gliotoxin in infected tissues or in immune tissues the connection between fungal infections, gliotoxin and immunosuppression will remain circumstantial.

Ochratoxins

The mycotoxin ochratoxin A (OA) is commonly produced by the molds *Aspergillus ochraceus* Wilhelmand *Penicillium verrucosum* Dierckx (Frisvad & Samson, 1991) and has been found worldwide as a food contaminant. Ochratoxin A is a potent nephrotoxin that has been detected in the blood and tissues of swine and poultry. It is known to cause porcine nephropathy and it may be associated with a fatal human kidney disease endemic to the Balkan region, although conclusive evidence has yet to prove this connection. The biochemical effects of OA include inhibition of macromolecular synthesis, increased lipid peroxidation, and inhibition of mitochondrial respiration (Kuiper-Goodman & Scott, 1989; Marquardt & Frohlich, 1992). Previous reviews of mycotoxin-induced immunotoxicity indicated that OA acts on more than one aspect of the immune system (Pestka & Bondy, 1994; Richard, 1991; Thurston et al., 1986), which parallels its multiple effects at the cellular level.

Older studies indicate that ochratoxin A inhibits humoral, cellular, and innate immune responses in poultry, including cellular depletion of lymphoid organs in broiler chicks (Dwivedi & Burns, 1984a, 1985; Farshid & Rajan, 1992), depressed delayed hypersensitivity responses in turkeys (Dwivedi & Burns, 1985), depressed serum immunoglobulin concentrations in broiler chicks (Dwivedi & Burns, 1984b), and depressed blood monocyte phagocytic activity in turkey poults (Chang & Hamilton, 1980). Recent studies have focused on potential interactions between OA and concurrent exposure to infectious agents associated with poultry disease and mortality. There are conflicting data on the effects of OA exposure on chicks challenged with *Salmonella typhimurium.* Elissalde et al. (1994) found that OA (3 mg/kg in diet for up to 3 wk) suppressed peripheral blood lymphocyte proliferation in response to PHA and ConA; however, *S. typhimurium* cecal colony counts were unaffected. In contrast, Fukata et al. (1996) found that duodenal and cecal *S. typhimurium* colony counts were significantly higher than controls in chicks given a

single oral dose of OA (3 mg/kg/bird). Differences in experimental design undoubtedly account for these apparently contradictory results. Elissalde et al. (1994) fed chicks 3 mg/kg OA for 7 d, followed by inoculation with 10^8 colony-forming units (CFU) of *S. typhimurium,* and finally followed by 7 to 9 additional days of OA exposure before cecal colony counts were determined. Fukata et al. (1996) administered twice the dose of *S. typhimurium* (10^8 CFU on 2 consecutive days), followed 24 h later with a single oral dose of 3 mg/kg/bird OA, and finally followed by cecal and duodenal colony counts at 7 and 12 h after OA administration. Both the doubled *S. typhimurium* inoculation and the reduced time between inoculation and colony counts could have been responsible for the increased colony counts seen by Fukata et al. (1996) compared to Elissalde et al. (1994). However, apparently in the short term OA can increase the susceptibility of chicks to *S. typhimurium* colonization, but colony counts may decline over a period of days even with constant exposure to OA in feed. This remains to be clarified experimentally. The ability of OA exposure to increase susceptibility to infectious agents has been confirmed by the observation that chicks infected with inclusion body hepatitis (IBH) virus and concurrently exposed to OA (0.5 ppm for up to 35 d) had more pronounced hematological, biochemical, and histopathological changes than chicks exposed to the virus or to OA alone (Sandhu et al., 1995, 1998).

When pigs ingested 2.5 mg OA/kg feed for 35 d, cell-mediated and phagocytic cell responses were suppressed (Harvey et al., 1992). Cutaneous basophil hypersensitivity to PHA was decreased after 24 h. Delayed hypersensitivity to tuberculin was suppressed in OA-treated gilts at 48 h but not at 24 or 72 h. In peripheral lymphocyte cultures, PHA-stimulated proliferation and ConA-stimulated IL-2 production were both suppressed in OA-treated pigs. Changes in anti-chicken RBC antibody titers or antibody isotypes, which would be indicative of humoral effects, were not observed in OA-treated pigs (Harvey et al., 1992).

Administration of OA to mice has been shown to be immunosuppressive, although the literature indicates that there are inconsistencies in responses based on route of administration, as well as discrepancies between dose and response in different studies. In mice given OA ip for up to 17 d (1 to 6 mg OA/kg body weight/d), changes included decreased phagocytosis in circulating phagocytic cells, decreased splenic antibody-producing cells, and serum antibody titers to SRBC and *Pasteurella multocida.* Parameters that were unchanged included numbers of circulating lymphocyte subpopulations, measured by flow cytometry, and cell-mediated immunity, measured by changes in foot-pad swelling responses to SRBC or *Pasteurella* antigen. Significant changes occurred at either 3 or 6 mg OA/kg body weight (Müller et al., 1995). Although the dosing period was shorter, the toxin levels causing statistically significant changes were within range of those used by Prior and Sisodia (1982), who observed

suppressed antibody responses to *Brucella abortus* antigen at doses of 5 mg/kg body weight after 50 d of ip OA administration. In contrast, single ip injections of 0.005 µg OA/kg body weight (Haubeck et al., 1981) or 1 µg OA/kg body weight (Creppy et al., 1983) inhibited antibody responses to SRBC. These doses are comparatively lower than the levels of OA required to elicit immunotoxic responses in mice and in other animal models, and have yet to be reconciled with the current literature.

Until recently the literature indicated that oral exposure to OA was not effective in generating immunotoxicity in mice. Antibody responses to *Brucella abortus* antigen were actually increased in mice exposed to OA in feed (50 d, 4 ppm; Prior & Sisodia, 1982), whereas ip administration of OA to mice suppressed antibody responses to SRBC (single dose, 1 µg/kg body weight; Creppy et al., 1983) and *Brucella abortus* antigen (50 d, 5 mg/kg body weight; Prior & Sisodia, 1982). However, recent research indicates that immune suppression does occur in mice exposed to OA orally. Antibody responses to SRBCs were suppressed in mice receiving 250 or 2600 µg OA/kg diet for 28 d; after 90 d of dietary OA exposure mice had lower proportions but not lower total numbers of thymic CD4+ and CD8+ cells (250 and 2600 µg OA/kg diet) and decreased spleen and thymus lymphocyte proliferative responses to ConA (6, 250, and 2600 µg OA/kg diet) (Thuvander et al., 1995). Several aspects of peritoneal macrophage function were compromised in mice receiving a daily oral dose of OA for 17 wk (1.5 mg/kg body weight), including chemotactic activity, IL-1α, and TNF-α production (Dhuley, 1997).

Ochratoxin A administered to pregnant female rodents either ip or by gavage at doses ranging from 1 to 10 mg/kg body weight causes fetal mortality and a range of developmental abnormalities in pups, including skeletal malformations and brain, central nervous system, craniofacial, and ocular abnormalities (Kuiper-Goodman & Scott, 1989). Prenatal exposure to lower doses of OA has been shown to affect the immune system of developing mice and rats (Thuvander et al., 1996a, 1996b, 1996c). In a short-term mouse study a single oral dose of OA (10, 50, or 500 µg/kg body weight) given to dams at 4 d pregestation caused decreased thymic CD4+, increased CD4+CD8+ lymphocyte subpopulations, and suppressed splenic and thymic lymphocyte proliferation to ConA and LPS in pups sampled at 15 d postpartum. On d 32 postpartum, pup antibody responses to SRBC were unaffected. All significant changes were seen primarily at the two highest OA doses (Thuvander et al., 1996c). In multidose mouse studies, dams were exposed to OA (0.18, 30, or 200 µg OA/kg feed) for 2 wk prior to mating and for the entire gestation period. Pups had higher thymus weights and cell numbers accompanied by increased numbers of CD4+, CD8+, and CD4+CD8+ cells (200 µg/kg feed) and decreased splenic CD4+ and CD8+ cells (200 µg/kg feed) when sampled at 14 d postpartum. Spleen and thymus lymphocyte proliferative responses to LPS and ConA were unaffected, as were antibody responses to SRBC and the

viral antigen PR8 and NK cell activity (Thuvander et al., 1996a). A similar study with rats indicated that while prenatal exposure to OA affected immune function in pups, there were apparent species-related differences in immune responses. Rat dams were exposed to OA (50 μg/kg body weight) by gavage throughout gestation. In contrast to mice, thymus weights and cellularity were unaffected but spleen proliferative responses to LPS were depressed in rat pups sampled at 14 d and 13 wk. Natural killer cell activity and antibody responses to influenza antigen PR8 were unaffected (Thuvander et al., 1996b).

In rodents, exposure to OA during lactation results in transient immunostimulation (Thuvander et al., 1996b, 1996c), demonstrating that OA is not wholly immunosuppressive. In mice a single oral dose of 500 μg OA/kg body weight administered to dams at 10 d postpartum resulted in a transient increase in ConA and LPS-induced pup spleen lymphocyte proliferation 72 h after dams were given OA. This effect was not observed in pups 14 d after dams were given OA (Thuvander et al., 1996c). In rats there were increased numbers of thymocytes at d 14 postpartum in pups from dams given 50 μg OA/kg body weight (Thuvander et al., 1996b). In contrast to mice, LPS-induced spleen lymphocyte proliferation was decreased at the highest dose (250 μg OA/kg body weight in dams); however, ConA-induced proliferative responses in splenic and thymic lymphocytes were elevated at lower OA exposure levels (10 and 50 μg/kg body weight in dams) (Thuvander et al., 1996b). Longer term studies with rats exposed during lactation or during both gestation and lactation failed to reproduce the same degree of immunostimulation. Splenocyte numbers were depressed at d 14 in rats exposed to OA during lactation and during gestation/lactation via a single daily oral dose of OA (50 μg/kg body weight) given to dams. Splenic and thymic lymphocyte proliferation were unaffected in all rats at 14 d postpartum, but at 13 wk postpartum rats exposed to OA during gestation and lactation had increased splenic lymphocyte proliferation using 9 μg/ml but not 22 μg/ml LPS. Natural killer cell activity and antibody responses to influenza antigen PR8 were unaffected (Thuvander et al., 1996b). The observation of immunosuppression in rodents exposed prenatally to OA and transient immunostimulation in rodents exposed during lactation highlights the complex nature of interactions between OA and the developing immune system. This suggests a need for further studies of immune responses in adult animals exposed perinatally to OA.

In vitro OA has been shown to abolish human B- and T-lymphocyte proliferation and to inhibit IL-2R expression and IL-2 production in T lymphocytes (Lea et al., 1989). Furthermore, OA was shown to inhibit the late stages of T-cell activation such as IL-2-induced proliferation, but not the early stages, for example, increased cytoplasmic Ca^{2+} levels or activation of protein kinase C (Størmer & Lea, 1995). These events could be connected to the ability of OA to inhibit both DNA and protein synthesis under certain conditions. Ochratoxin A has also been shown to induce

DNA degradation associated with apoptosis in PHA-stimulated human blood lymphocytes (Seegers et al., 1994), indicating the potential involvement of programmed cell death in OA-induced immunotoxicity.

Patulin

Although the fungal secondary metabolite patulin has been most commonly associated with moldy apples and products made from moldy apples, this toxin is produced by several members of the fungal genera *Penicillium* and *Aspergillus* that can contaminate a variety of foods and feeds (Harwig et al., 1973; Stott & Bullerman, 1975). Past studies, primarily using mice, indicated variable effects of patulin on the immune system. These effects included increased numbers of splenic T lymphocytes and depressed serum immunoglobulin concentrations (Escoula et al., 1988b), depressed delayed hypersensitivity responses (Paucod et al., 1990), and increased neutrophil numbers and resistance to *Candida albicans* infection (Escoula et al., 1988a). A thorough battery of immunotoxicity endpoints has been examined in mice administered patulin daily by gavage for 28 d at doses of 0.08 to 2.56 mg patulin/kg body weight (Llewellyn et al., 1998). These doses were calculated to approximate estimated human exposure levels. Changes in immune cell numbers included depressed peripheral blood leukocyte and lymphocyte numbers (1.28 and 2.56 mg patulin/kg), increased numbers of splenic monocytes and NK cells (0.08 mg patulin/kg), increased numbers of splenic cytotoxic T lymphocytes (2.56 mg/kg), and changes in the percentages of immunoglobulin (Ig)+, CD3+, CD4+CD8–, and CD4–CD8+ in spleen. These changes in cell numbers did not reflect functional changes. There were no measurable changes in immune function in patulin-treated mice using the following endpoints: antibody responses to SRBC; mixed leukocyte responses; and natural killer cell function. The authors concluded that exposure to patulin at levels consistent with potential human exposure in foods would not likely alter immune responses (Llewellyn et al., 1998).

Trichothecenes

The trichothecenes are a group of over 180 sesquiterpenoids that are produced by *Fusarium, Stachybotrys, Myrothecium,* and other fungal genera (Grove, 1993, 1996) and include some of the most potent protein synthesis inhibitors known (Bamburg, 1983). The trichothecene family is divided into four groups (A through D) based on modifications to the parent trichothecane ring system (Ueno, 1987). Vomitoxin (DON; deoxynivalenol; group B), nivalenol (group B), T-2 toxin (group A), and diacetoxyscirpenol (group A) are among the most common trichothecenes detected in cereal grains (Rotter et al., 1996; Ueno, 1987). These compounds have been associated with human and animal toxicoses that are sometimes fatal (Bhat et al., 1989; Coté et al., 1984; Joffe, 1978, 1983; Ueno, 1983). Experimentally, acute oral exposure to trichothecene myco-

toxins causes severe damage to actively dividing cells in bone marrow, lymph nodes, spleen, thymus, and intestinal mucosa. Thus, leukocytes and the immune system are a primary target for trichothecenes.

Depending on dose and exposure regimen, trichothecenes can be both immunosuppressive and immunostimulatory. Repetitive exposure to trichothecenes increases susceptibility to a diverse array of pathogens that include *Mycobacterium* (Kanai & Kondo, 1984), *Candida* (Salazar et al., 1980), *Cryptococcus* (Fromentin et al., 1981), *Listeria* (Corrier et al., 1987b), *Salmonella* (Sugita-Konishi et al., 1998; Tai & Pestka, 1988a, 1990; Vidal & Mavet, 1989), *Aspergillus* (Niyo et al., 1988a, 1988b), and herpes simplex virus type I (Friend et al., 1983). A five log reduction in LD50 for *Salmonella* occurs in mice that have been orally coadministered with T-2 toxin (Tai & Pestka, 1988a). There is a marked increase in susceptibility to LPS when coadministered with trichothecenes, suggesting that impaired resistance to LPS might be one mechanism for increased susceptibility to gram-negative pathogens (Tai & Pestka, 1988b; Zhou et al., 1999). Taylor et al. (1989, 1991) postulated that T-2 toxin treatment enhances LPS absorption from the gut and that this produces some of the pathologic sequelae associated with T-2 toxicosis. In contrast to reports of immune suppression, resistance to mastitis-causing pathogens is enhanced when mice are administered T-2 toxin by gavage prior to experimental infection (Cooray & Jonsson, 1990). Short-term preinoculation with T-2 toxin also enhances resistance to *Listeria,* whereas postinoculation with T-2 toxin results in immunosuppression (Corrier & Ziprin, 1986a, 1986b; Corrier et al., 1987a, 1987b). Corrier (1991) suggested that enhanced resistance is associated with increased migration of macrophages and elevated phagocytic activity and further hypothesized that these latter effects may have been mediated by altered T regulatory cell activity.

Depending on dose, trichothecene exposure in vitro impairs or enhances mitogen-induced lymphocyte proliferation (Atkinson & Miller, 1984; Bondy et al., 1991; Cooray, 1984; Hughes et al., 1988, 1989, 1990; Miller & Atkinson, 1986, 1987; Tomar et al., 1986, 1987, 1988a). The rank order of potency among trichothecene classes for in vitro inhibition of rodent and human lymphocyte proliferation assays is macrocyclic (for example, roridins and verrucarins) > type A group (for example, T-2 toxin and diacetoxyscirpenol) > type B group (for example, vomitoxins and nivalenol) (Bondy et al., 1991; Forsell et al., 1985; Forsell & Pestka, 1985; Hughes et al., 1988, 1990; Lee & Li, 1999; Mekhancha-Dahel et al., 1990; Pestka & Forsell, 1988; Thompson & Wannemacher, 1986; Tomar et al., 1988b).

In vitro lymphotoxicity of the type A and type B trichothecenes apparently depends on the degree of acylation in substituent groups. Forsell et al. (1985) observed that metabolism of the parent trichothecene T-2 toxin altered the antiproliferative effects on human lymphocytes. The results suggested that the initial hydrolysis of T-2 toxin and the hydroxylation of

T-2 toxin to 3′-OH T-2 toxin did not significantly decrease the immunotoxicity of the parent molecule, whereas further hydrolysis to T-2 triol and T-2 tetraol toxins or hydroxylation to 3′-OH HT-2 toxin decreased in vitro toxicity. Porcher et al. (1988) proposed that differences in sensitivities exist among lymphocyte cell types and related this to both differences in uptake and metabolism to less toxic compounds. However, evidence supporting this proposal has not accumulated. Trichothecenes are also cytotoxic to macrophages (Gerberick & Sorenson, 1983; Gerberick et al., 1984).

Trichothecenes can stimulate and impair humoral immunity. Rosenstein et al. (1981) first observed that repeated ip injection of T-2 toxin caused a decreased humoral response to T-dependent antigens but an increased response to T-independent antigens. In vitro exposure to T-2 inhibits the plaque-forming cell (PFC) response to T-cell-dependent and -independent antigens (Holt & DeLoach, 1988). Dietary exposure of CD-1 mice to 3-acetyldeoxynivalenol or T-2 toxin does not alter T-cell-independent antibody responses to DNP-Ficoll or *E. coli* LPS, but at 10 ppm they enhance the T-cell-dependent response to SRBC (Tomar et al., 1987, 1988b). Female CD-1 mice fed T-2 toxin (3 ppm) for 16 mo have enhanced plaque forming cell (PFC) responses to sheep red blood cells (Schiefer et al., 1987). Prenatal exposure to T-2 toxin on d 11 of gestation does not impair immunity in CD1 mice (Blakley et al., 1986). Macrocyclic trichothecenes injected ip depress murine antibody response to SRBC. Oral gavage with T-2 toxin results in increased spontaneous antibody-producing cells for all isotypes in the spleen (Cooray & Lindahl-Kiessling, 1987). Deoxynivalenol (DON) in the diet at a 10 ppm threshold or given by gavage at 0.75 mg/kg body weight can similarly impair the murine splenic PFC response to SRBC (Pestka et al., 1987; Robbana-Barnat et al., 1988; Tryphonas et al., 1986).

One of the most dramatic effects of DON is a pronounced elevation in serum immunoglobulin A (IgA) and concurrent depression in IgM and IgG that is found in mice exposed to DON in feed (Forsell et al., 1986). The threshold for this inductive effect is 2 ppm, with maximal effects occurring in the 10–25 ppm range (Dong et al., 1991; Pestka et al., 1989, 1990b, 1990c). Increased serum IgA appears concomitantly with elevated IgA immune complexes and polymeric IgA. Peyer's patch lymphocytes and to a lesser extent splenic lymphocytes isolated from mice fed DON produce significantly more IgA than those cultures derived from mice receiving ad libitum or restricted control diets (Pestka et al., 1989, 1990a, 1990d; Bondy & Pestka, 1991). These results suggest that DON enhances differentiation to IgA-secreting cells at the Peyer's patch level and that this impacts the systemic compartment. Dietary DON can also drive IgE elevation in mice (Pestka & Dong, 1994).

The immunopathology associated with DON-induced dysregulation of Ig production is very similar to human IgA nephropathy (Berger's disease), the most common glomerulonephritis worldwide (D'Amico, 1987). In addition to IgA hyperelevation, mice exposed to DON exhibit mesan-

gial IgA accumulation and hematuria, which are hallmarks of IgA nephropathy (Dong et al., 1991). These effects can persist long after withdrawal of DON from the mouse diet (Dong & Pestka, 1993). Human IgA nephropathy occurs to a greater extent in males than females and in the B6C3F1 mouse; males exhibit a predilection for DON-induced IgA nephropathy in terms of threshold toxin dose, as well as onset and magnitude of response (Greene et al., 1994a, 1994b, 1995). Another common feature of the human disease and the murine model is the involvement of polyvalent "natural" IgA, which may be associated with immune complex formation and the subsequent glomerulonephritis (Rasooly & Pestka, 1992, 1994; Rasooly et al., 1994; Yan et al., 1998a). Intermittent DON exposure is less effective at inducing IgA nephropathy than continuous exposure (Banotai et al., 1999b). Dietary DON can induce IgA nephropathy in murine models of systemic lupus erythematosus but does not exacerbate the manifestations of lupus (Banotai et al., 1999a). Dietary nivalenol has also been shown to induce IgA nephropathy in mice (Hinoshita et al., 1997).

What are the mechanisms by which trichothecenes can both suppress and stimulate immune function? It is now apparent that high doses of trichothecenes promote rapid onset of leukocyte apoptosis, and this will undoubtedly be manifested as immunosuppression. Using flow cytometric analysis, Pestka et al. (1994) first observed that DON either inhibits or enhances apoptosis in a concentration-dependent manner in T cells, B cells, and IgA^+ cells isolated from spleen, Peyer's patches, and thymus. Induction of apoptosis was dependent on lymphocyte subset, tissue source, and glucocorticoid induction. The human promyelotic cell line HL-60 is similarly susceptible to T-2 toxin-induced apoptosis (Ueno et al., 1995). These in vitro results are relevant to the whole-animal model since in vivo administration of trichothecenes to rodents results in apoptosis in thymus, spleen, bone marrow, and liver (Ihara et al., 1997, 1998; Miura et al., 1998; Shinozuka et al., 1997a, 1997b, 1998). Using adrenalectomized mice and anti-TNF-α antibody-injected mice, Islam et al. (1998a) demonstrated that neither endogenous glucocorticoid nor TNF-α appeared to be involved in T-2 toxin-induced thymocyte apoptosis. When Islam et al. (1998b) investigated the effect of chemical structure(s) of T-2-derived metabolites on the induction of thymic apoptosis in vivo in mice, it was observed that both the acetyl group at the C-4 position and the isovaleryl or 3′-hydroxyisovaleryl group at the C-8 position of the T-2 molecule were critical for the effect. These results were consistent with the aforementioned blastogenesis studies of Forsell et al. (1985) using human lymphocytes.

Trichothecene-induced apoptosis also occurs in tissues of the gastrointestinal tract including the gastric mucosa, gastric glandular epithelium, and intestinal crypt cell epithelium (G. Li et al., 1997; J. Li et al., 1997a; J. Li & Shimizu, 1997). Apoptotic loss in these tissues might result in the breakdown of nonspecific mucosal defense mechanisms such as the epithe-

lial barrier and mucus secretion and thus result in increased translocation of gut bacteria and endotoxin.

In contrast to apoptosis, exposure to low levels of trichothecenes appears to promote expression of a diverse array of cytokines in vitro and in vivo (Azcona-Olivera, 1995a, 1995b; Dong et al., 1994; Holt et al., 1988; Ji et al., 1998; Warner et al., 1994; Wong et al., 1998; Zhou et al., 1997, 1998, 1999). These cytokines have the potential to both upregulate and downregulate a wide array of immune functions. Trichothecenes and other protein synthesis inhibitors stimulate IL-1 production by macrophages (Miller & Atkinson, 1986; Mizel & Mizel, 1981) and IL-2 formation by lymphocytes (Efrat et al., 1984; Holt et al., 1988). Sherman et al. (1987) identified cardiovascular lesions in rats that had received splenic cells from syngeneic rats treated with T-2 toxin and suggested that this may be mediated by IL production.

Deoxynivalenol-induced aberrant IgA production may be mediated through superinduction of cytokine gene expression in T helper (TH) cells, and among these, the effects on IL-2 by DON are pronounced in both in vitro and in vivo models (Azcona-Olivera et al., 1995a, 1995b; Dong et al., 1994; Ouyang et al., 1995, 1996a; Warner et al., 1994). Using an ex vivo approach and neutralizing antibodies, Yan et al. (1997) found that potential for enhanced IgA production exists in lymphocytes as early as 2 h and as late as 24 h after a single oral exposure to DON, and this may be related to the increased capacity to secrete the helper cytokines IL-2, IL-5, and IL-6. Both CD4+ and macrophage cells appear to be involved in this process (Yan et al., 1998b). Thus, superinduction of cytokine expression may, in part, be responsible for upregulation of IgA secretion in mice exposed orally to DON.

The specific molecular mechanisms for the cytokine superinduction by DON are incompletely understood. Based on studies with cycloheximide, it has been hypothesized that superinduction of IL-2 gene expression by DON is mediated via both transcriptional and/or posttranscriptional mechanisms. Transcriptional mechanisms involving the transcription factors nuclear factor-κB (Ouyang et al., 1996b) and activator protein-1 (Li et al., 2000) have been described in EL-4 cells exposed to DON. Using transcriptional inhibitors, J. Li et al. (1997b) also found that the superinduction of IL-2 mRNA expression by DON was due, in part, to markedly increased IL-2 mRNA stability.

There is increasing evidence that trichothecenes can be encountered as airborne contaminants. Macrocyclic trichothecenes are produced by *Stachybotrys* during growth on cellulose-containing building materials such as wall paper and gypsum board liner under conditions of high moisture and can be distributed in the air via spores (Nielsen et al., 1998a, 1998b; Nikulin et al., 1994). Because the fungus can contaminate buildings subjected to recurrent water damage from air-conditioning condensation or leakage, there has been growing concern about the health of occupants of

Stachybotrys-contaminated buildings (Cooley et al., 1998; Sorenson et al., 1987). Johanning et al. (1996) reported that disorders of the immune, respiratory, and central nervous systems and mucous membranes occurred in people exposed in a water-damaged office environment to *Stachybotrys chartarum*-produced macrocyclic trichothecenes such as satratoxins. Similarly, outbreaks of building-related diseases including recurrent cough, irritation of the eyes and skin, mucous membrane disorder, respiratory symptoms, headache, and fatigue have been reported to be associated with this fungus (Croft et al., 1986; Dales et al., 1991; Dearborn et al., 1997; Etzel et al., 1998; Ruotsalainen et al., 1995; Smith et al., 1992; Smoragiewics et al., 1993). Recent studies of fatal pulmonary hemosiderosis in Cleveland infants reported a strong association between the incidence of this syndrome and the levels of *Stachybotrys* found in case homes (Dearborn et al., 1997; Etzel et al., 1998; Jarvis et al., 1998).

The immune system might be a target in these *Stachybotrys*-associated illnesses. To evaluate the capacity of these *Stachybotrys* mycotoxins to alter immune function, the effects of satratoxin G, H, and F, roridin A, and verrucarin A on IL-2 production and proliferation were evaluated in a murine T-cell model (Lee & Li, 1999). EL-4 thymoma cells were stimulated with phorbol 2-myristate 13-acetate and ionomycin and concurrently exposed to various concentrations of the trichothecenes. Interleukin-2 concentrations measured by enzyme-linked immunosorbent assay (ELISA) in culture supernatants at 24 and 72 h were significantly increased in cultures that were incubated with 0.5 to 1 ng/ml of satratoxin H, 1 to 5 ng/ml of isosatratoxin F, 0.1 to 0.5 ng/ml of roridin A, or 0.25 to 0.5 ng/ml of verrucarin A. However, IL-2 levels at these time points were significantly depressed when incubated in the presence of higher concentrations of satratoxin G (≥2.5 ng/ml), satratoxin H and isosatratoxin F (≥5 ng/ml), and roridin A and verrucarin A (≥1 ng/ml). Cell proliferation and viability, as measured by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, were depressed by each of the trichothecenes in a concentration-response fashion. MTT responses were significantly decreased by as little as 0.5 ng/ml of satratoxin G, roridin A, and verrucarin A and by 2.5 ng/ml of isosatratoxin F and satratoxin H. When these data were compared to those from EL-4 cells exposed to DON, the macrocyclic trichothecenes were at least 100 times more potent. The results indicate that, at low doses, macrocyclic trichothecenes as a group could superinduce IL-2 production even while partially suppressing proliferation, whereas higher concentrations suppressed both cytokine production and proliferation. The capacity of these compounds to dysregulate cytokine production in a biphasic fashion may play an etiologic role in outbreaks of human illness associated with indoor *Stachybotrys* contamination.

Trichothecene-induced immunosuppression is most readily explained by the capacity of these compounds to bind to ribosomes and inhibit protein synthesis (Bamburg, 1983; Rosenstein & Lafarge-Frayssinet, 1983). Other

toxic mechanisms that have been suggested to result from trichothecenes include impaired membrane function (Bunner & Morris, 1988), altered intercellular communication (Jone et al., 1987), and deregulation of calcium (Yoshino et al., 1996). Results of recent studies suggest that early alterations in cell signaling seem to be critical. A "ribotoxic stress response" has been demonstrated for translation inhibitors such as anisomycin, ricin, and α-sarcin (Iordanov et al., 1997). In this model, alteration of 28s rRNA by these inhibitors was postulated to be an initiation signal for activation of SAPK/JNK, which is a MAP kinase (MAPK). Increased MAPK activity could drive activation of transcription factors that promote cytokine production as well as induce apoptosis. Another possible intermediate signal between trichothecene mycotoxins and MAPK activation is the generation of reactive oxygen species. Trichothecene mycotoxins cause lipid peroxidation, and their toxic effects can be inhibited by antioxidants such as vitamin E and *N*-acetylcysteine (Rizzo et al., 1994). Hydrogen peroxide induces activation of several MAPKs as well as apoptosis (Wang et al., 1998). This oxidative stress-induced apoptosis is markedly potentiated when activation of the kinase ERK is selectively inhibited by PD98059 (Aikawa et al., 1997; Wang et al., 1998). Inhibition of SAPK/JNK activation by the expression of a dominant negative mutant form of SAPK/JNK kinase decreases oxidative stress-induced apoptosis, whereas inhibition of p38 MAPK activity with p38-specific inhibitors SB202190 and SB203580 has no effect on cell survival (Wang et al., 1998). These results are very similar to the characteristics of trichothecene-induced MAPK activation and apoptosis, which supports the possibility of the involvement of oxidative stress. Nevertheless, the possibility of cross-talk between reactive oxygen species and ribotoxic stress signals cannot be excluded in an explanation of the mechanism of trichothecene-induced MAPK activation.

The most toxic trichothecenes are generally considered the most potent inhibitors of protein synthesis (Ueno, 1987). Recently, Shifrin and Anderson (1999) evaluated the capacities of different trichothecene mycotoxins to activate SAPK/JNKs and p38 MAPK and induce apoptosis. They suggested that protein synthesis inhibition efficiency capacity did not correlate with SAPK/JNK and p38 MAPK activation and apoptosis. Further, highly toxic trichothecenes such as T-2 toxin and verrucarin A did not cause activation of SAPK/JNK and p38 MAPK or initiate apoptosis, whereas less toxic trichothecenes such as T-2 tetraol, DON, and nivalenol did. In contrast, Yang et al. (2000) observed a close correlation in protein synthesis inhibition capacity, MAPK activation, and apoptosis in macrophages among a number of trichothecenes examined. These opposing results might relate to differences in toxin concentrations used in the two studies. Shifrin and Anderson (1999) used the relatively high concentration of 3.8 μ*M* for T-2 toxin and verrucarin A (1.77 μg/ml and 1.91 μg/ml, respectively), which was 200 to 400 times higher than the concentrations used by Yang et al. (2000). This high concentration might have driven a very rapid onset of

MAPK activation and apoptosis. When volumetric aliquots of cell extracts were tested 3 h later, they were likely to be devoid of MAPK signal or DNA laddering because most of the cells had undergone apoptosis. Thus, the observation that MAPK activation correlated with cytotoxicity and apoptosis is likely to be the more accurate representation of the comparative apoptotic effects of trichothecenes.

Taken together, numerous in vitro and in vivo studies have demonstrated that trichothecenes can affect leukocytes by deregulating cytokine production and by inducing apoptosis. The transition between these two effects occurs with increasing concentration/dose of trichothecene, with the net effects being immune stimulation or suppression, respectively. From a practical perspective, type A or B trichothecenes at dietary concentrations of a few parts per million are sufficient to affect immune function in a variety of experimental models. However, little is known of either the minimal levels of the much more toxic satratoxins required to alter immunity or the relevance of airborne exposure to immune function.

FUTURE RESEARCH

The diversity of future research in the area of fungal toxin immunotoxicity will undoubtedly reflect the structural and mechanistically diverse nature of these compounds. Based on the studies surveyed in this review, the following data gaps were identified:

1. For trichothecenes, some progress has been made in exploring the molecular basis of immunomodulation; however, for most fungal toxins there is need for further exploration in this area. In particular, further studies of the signal transduction pathways involved in fumonisin-induced immunomodulation could provide valuable insight into the role of sphingolipid metabolism in immune function.
2. The interaction of fungal toxins with elements of the mucosal immune system has been explored for DON but not for other fungal toxins.
3. Data on the immunomodulatory effects in offspring of pre- and perinatal exposure to fungal toxins, similar to studies of OA, would be valuable for other fungal toxins.
4. The role of cell signaling deregulation in evoking effects on leukocytes in vitro and in vivo as well as development of quantitative structure–activity relationships among trichothecene mycotoxins requires further research.
5. A major gap in research on the immunotoxicity of fungal toxins lies in the absence of data on potential immunomodulation by commonly occurring mixtures of toxins. Typically, several mycotoxins may be present in a contaminated food or feed. For example, combinations of aflatoxin, trichothecenes, and/or fumonisins have been found as simultaneous contaminants of corn (Chamberlain et al., 1993; Chu & Li,

1994). The combined effects of several potential immunotoxins, all with different mechanisms of toxicity, are unknown.

6. The immunomodulatory interactions between fungal toxins and stressors such as infectious agents or modulators such as nutritional factors deserve further consideration. In particular, the possibility that livestock or poultry may be protected from mycotoxin-induced immunotoxicity by supplementing or manipulating feed components should provide economic incentive for this research.
7. The capacity of airborne mycotoxins to exert subtle immunotoxic effects on an exposed population merits further consideration, as evidenced by the recent concerns over *Stachybotrys*-contaminated air sources. Airborne mycotoxins can occur as contaminants of indoor air when fungi grow on building materials or as part of organic dusts that are generated during agricultural activities.

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